Remarks

Based on the amendments to the claims and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Status of the Claims

Claims 8-13, 56 and 70-75 are at issue and are present for examination. Claim 8 is the sole independent claim. Claims 8, 9, and 70-75 are sought to be amended. Support for the amendments to the claims can be found throughout the specification as filed. No new matter has been introduced.

II. Summary of the Interview of December 4, 2003

Applicants' representative would like to express his appreciation of the helpful suggestions provided by Examiner Hutson during the personal interview of December 4, 2003. During the interview, all outstanding rejections were discussed. The Examiner indicated that inclusion of an active RNA degradation step would obviate the rejection under 35 U.S.C. § 112, second paragraph, and would also distinguish the presently claimed invention from the documents cited under 35 U.S.C. § 102. The rejection under 35 U.S.C. § 103(a) was discussed, in particular, the motivation to combine the cited documents was discussed.

III. Summary of the Office Action

In the Office Action dated August 18, 2003, the Examiner made 5 rejections of the claims. Applicants respectfully offer the following remarks to overcome these rejections.

IV. The Rejection of Claims 8-13, 56 and 70-75 Under 35 U.S.C. § 112, Second Paragraph Must be Withdrawn

In the Office Action at pages 2-3, claim 8 and claims dependent thereupon 9-13, 56, and 70-75, were rejected as indefinite for the recitation of "incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said double-stranded DNA and sufficient to degrade single-stranded RNA." The Examiner asserted that this recitation is indefinite in view of Applicants' arguments that the documents cited against these claims do not teach the degradation of single stranded RNA. In the Examiner's view, the claims do not necessitate that single-stranded RNA be degraded, merely that the claimed mixture be incubated under conditions "sufficient to degrade" single-stranded RNA. Further, the Examiner asserted that the inclusion of RNaseH in dependent claim 9 added to the confusion in that RNaseH is specific for RNA:DNA hybrids and does not degrade single-stranded RNA.

The relevant portion of claim 8 has been amended to read as follows: b) incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said double-stranded DNA and ~~sufficient to~~ under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA. In addition, claim 9 has been amended to delete RNaseH. Applicants submit that

the claims as presently written are not indefinite and respectfully request reconsideration and withdrawal of this rejection.

V. The Rejection of Claims 8, 9, 10, 13, and 71-73 Under 35 U.S.C. § 102(b) as Being Anticipated by Davey et al. Must be Withdrawn

In the Office Action at pages 4-6, claims 8, 9, 10, 13, and 71-73 were rejected under 35 U.S.C. §102(b) as being anticipated by Davey, *et al.* (United States patent no. 5,409,818, hereinafter "Davey"). Applicants respectfully request reconsideration and withdrawal of this rejection.

As amended herein, claim 8 is drawn to a method for synthesizing a nucleic acid molecule from a preparation comprising RNA and double-stranded DNA, said method comprising: a) mixing the preparation with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity; and b) incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said double-stranded DNA and under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA. Claims 9, 10, 13, and 71-73 depend—directly or indirectly—from claim 8 and, thus, include conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA.

A claimed invention is anticipated under 35 U.S.C. § 102 only if there is "[d]isclosure in a single piece of prior art of each and every limitation of a claimed invention." *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 20, 57 USPQ2d 1057, 1061 (Fed. Cir. 2000), *citing Electro Med. Sys. S.A. v. Cooper Life Sciences,* 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994). Davey does not

disclose conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA and, therefore, does not anticipate the present invention.

In support of this rejection, the Examiner alleged that "Davey et al. does teach conditions sufficient to degrade single-stranded RNA. In order to anticipate the rejected claims it is unnecessary for any single stranded RNA to actually be degraded ... ." Office Action, page 5. Further, the Examiner asserted that "[n]o where in applicants claimed method is there a limitation that single-stranded RNA must be degraded." *Id.*

Applicants respectfully submit that this rejection is not applicable to the claims as presently written. The ribonuclease used by Davey is "specific for RNA-DNA hybrids." Davey, column 5, lines 34-35. Further, Davey states "[e]ach enzyme or enzyme preparation should be free of deleterious ribonuclease ("RNase") activities, with the exception of the preferred addition of a ribonuclease activity which is specific for hybrids of RNA and DNA (for example, ribonuclease H)." Davey, column 7, lines 17-22. Thus, Davey does not disclose conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA and, therefore, does not anticipate the present invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

VI. The Rejection of Claims 8, 9, 10, 13, and 72 Under 35 U.S.C. § 102(e) as Being Anticipated by Kenten et al. Must be Withdrawn

In the Office Action at pages 6-8, claims 8, 9, 10, 13, and 72 were rejected under 35 U.S.C. §102(e) as being anticipated by Kenten, *et al.* (United States patent no. 6,048,687, hereinafter "Kenten"). Applicants respectfully request reconsideration and

withdrawal of this rejection.

As discussed above, the method of claim 8 recites, *inter alia*, conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA. Claims 9, 10, 13, and 72 depend—directly or indirectly—from claim 8 and, thus, also require conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA.

A claimed invention is anticipated under 35 U.S.C. § 102 only if there is "[d]isclosure in a single piece of prior art of each and every limitation of a claimed invention." *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 20, 57 USPQ2d 1057, 1061 (Fed. Cir. 2000), *citing Electro Med. Sys. S.A. v. Cooper Life Sciences,* 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994). Kenten does not disclose conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA and, therefore, does not anticipate the present invention.

In support of this rejection the Examiner alleges that Kenten discloses conditions sufficient to degrade single-stranded RNA and "[n]o where in applicants claimed method is there a limitation that single-stranded RNA must be degraded." Office Action, page 7.

Applicants respectfully submit that this rejection is not applicable to the claims as presently written. The ribonuclease used by Kenten "hydrolyses RNA of an RNA-DNA hybrid without hydrolysing single or double-stranded RNA or DNA." Kenten, column 4, lines 20-22. Kenten refers to several publications for a detailed description of the amplification process used. See, Kenten, column 2, line 66, to column 3, line 4. One of these references (EP 0392 822-A2) is the European equivalent of the Davey patent

discussed above. Thus, the amplification method of Kenten is the same as that of Davey and, similarly, does not disclose conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA.

Applicants therefore respectfully submit that Kenten fails to disclose at least one element of the present claims and, therefore, Kenten does not anticipate the present claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

VII. The Rejection of Claims 70, 74, and 75 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Davey et al. Must be Withdrawn

In the Office Action at page 9, claims 70, 74, and 75 were rejected under 35 U.S.C. §103 as being obvious over Davey. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 70, 74, and 75 depend from claim 8. As discussed above, the method of claim 8 recites, *inter alia*, conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). In pertinent part, the MPEP states that "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP 2143.03, *citing In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). In addition, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings." MPEP 2143. Further, "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion to make the proposed modification." MPEP 2143.01 *citing In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention and respectfully request reconsideration and withdrawal of this rejection as it may be applied to the present claims.

As discussed above, Davey does not disclose conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA. Further, there is no suggestion in Davey to modify the conditions in order to make the peptides or polypeptides having ribonuclease activity degrade single-stranded RNA. Modifying the conditions of Davey so as to degrade single-stranded RNA would render Davey unsatisfactory for its intended purpose. The purpose of Davey is the amplification of specific nucleic acid sequences. Davey, Abstract. This is accomplished by converting a single-stranded RNA molecule into an double-stranded DNA molecule from which additional single-stranded RNA molecules can be transcribed. The transcribed single-stranded RNA molecules then serve as templates from which to produce additional double-stranded DNA molecules. See, Davey, Figure 1. In conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA, the input single-stranded RNA would be degraded as would the transcribed single-stranded RNA and no amplification would occur. Modifying the conditions of Davey to conditions under which said peptides or polypeptides having ribonuclease activity

degrade single-stranded RNA would render Davey unfit for its intended purpose; thus, there is no motivation to make such a modification of the conditions of Davey.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

VIII. The Rejection of Claims 8-12, 70, 71 and 73 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Major and Maudru et al. Must be Withdrawn

In the Office Action at pages 10-13, claims 8-12, 70, 71, and 73 were rejected under 35 U.S.C. §103 as being obvious over Major (*Biotechniques* 12(1):40-43, 1992, hereinafter "Major") and Maudru *et al.* (*J. Virological Methods* 66:247-261, 1997, hereinafter "Maudru"). Applicants respectfully request reconsideration and withdrawal of this rejection.

As discussed above, the method of claim 8 recites, *inter alia*, conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA. Claims 9-12, 70, 71, and 73 depend—directly or indirectly—from claim 8 and likewise require conditions under which said peptides or polypeptides having ribonuclease activity degrade single-stranded RNA.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). In pertinent part, the MPEP states that "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP 2143.03, *citing In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). In addition, "there must be some

suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." MPEP 2143. Further, when the teachings of a prior art reference are considered:

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied* 469 U.S. 851 (1984)

MPEP §2141.02

This rejection was previously stated in the Office Action of February 11, 2003, File Wrapper Paper 23. Major was cited as teaching a PCR method for screening point mutations and that "some primers, especially those with 3'-terminal T:T mismatch result in extra minor bands when bacterial colony lysates were used for the starting material" resulting in a decrease in sensitivity of the assay. File Wrapper Paper 23, paragraph bridging pages 7 and 8. Maudru was cited for the proposition that the background signal in a PCR-based RT assay is the result of an intrinsic RT activity of *Taq* DNA polymerase and that the background may be eliminated by the inclusion of ribonuclease in the assay. *Id.* at page 8, first full paragraph. The Examiner then asserted that one of skill in the art would have been motivated to combine the teachings of the two cited documents by a desire to reduce residual RNA in order to reduce the background signal from the PCR-based assay. *Id.* at page 8, second full paragraph.

In reiterating this rejection in the Office Action of August 18, 2003, the Examiner cited the following sentence from the abstract of Maudru "[t]he background signal of the PBRT assay was found to be due to an intrinsic RNA-dependent DNA polymerase activity of the Taq DNA polymerase, the enzyme used for the PCR." Office Action, page

11. The Examiner also quoted a passage from the text of Maudru as follows "The use of thermostable DNA polymerases that have low RNA-dependent DNA polymerase activity and the inclusion of an RNase incubation prior to the PCR amplivfication [sic] of the cDNA product effectively eliminated the background of the assay." *Id.* The Examiner then concluded one skilled in the art would have been motivated to add a ribonuclease to the method of Major by the desire to remove residual RNA sequence contamination from the targeted nucleic acid template and that this would increase the sensitivity of the PCR assay method from bacterial colony lysates. *Id.* at page 12.

Maudru is concerned with eliminating background reverse transcriptase activity in a PCR-based reverse transcriptase assay. Maudru first conducts a reverse transcription reaction with a potentially reverse transcriptase-containing sample using a test RNA template and an oligodeoxynucleotide primer that binds to the template. Maudru, pages 249-250, sections 2.1 through 2.2.1. Thus, in the assay mixture of Maudru a suitable substrate for an RT enzyme (*i.e.*, an RNA template and a DNA oligonucleotide) is present. After the reverse transcription reaction, any unreacted substrate is still present and capable of reacting with the intrinsic RNA-dependent DNA polymerase activity of the thermostable DNA polymerase used in the PCR amplification step of the assay. Thus, Maudru includes an RNase to eliminate this pre-formed substrate, thereby reducing the background of the assay.

In contrast to Maudru, Major is concerned with detecting a single point mutation in a plasmid using a simplified allele-specific PCR method. Major, page 40, first column. In this method, plasmid DNA is amplified using primers that differ in the 3'-nucleotide. Major, Figure 1. Thus, Major uses a DNA template and DNA

oligonucleotides in his assay. The small amount of background seen by Major is attributed to the mismatched 3'-nucleotides of the primer (see, Major, page 42, center column and first paragraph of right column) and was eliminated by the inclusion of a PCR enhancing reagent, Perfect Match. Major, page 42, center column.

One skilled in the art would have had no motivation to include an RNase in the method of Major. First, Major used a DNA template and DNA primers in a PCR assay. There is no teaching or suggestion in Major that RNA has any effect on the assay. In fact, Major compares the use of RNA containing bacterial lysates to the use of purified miniprep plasmid DNA (see Figure 2) and notes that "one can get single-base discrimination using unpurified template." Major, page 42, left column. In addition, Major attributes background in the assay to the mismatch of the 3'-nucleotide in the primer to the sequence to be amplified. One skilled in the art would not have considered the presence or absence of RNA likely to affect this background. Finally, Major teaches the use of a PCR enhancing compound to reduce spurious bands. Major, page 42, center column. One skilled in the art would have no motivation to add RNase to the assay of Major to reduce the background since Major already teaches how to reduce the background.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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